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SYSTEMATIC REVIEW

A Systematic Literature Review of Health-Related Quality of Life Outcomes and Associated Utility Values in Relapsed and/or Refractory Large B Cell Lymphoma

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Abstract

Background In this ever-expanding treatment landscape, there is a lack of consolidated health-related quality of life (HRQOL) outcomes and utility reports in relapsed or refractory (R/R) large B cell lymphoma (LBCL) to inform health care policy and decision-maker assessments for both old and new products. These assessments can have a direct effect on what treatment options are available to patients and physicians.

Objective A systematic literature review (SLR) was performed to understand the HRQOL evidence for treatments in R/R LBCL and identify associated health utility values.

Methods The SLR searched and screened literature published from 1 January 2003 to 2 May 2022. Studies were screened based on Population, Intervention, Comparator, Outcome, Study design criteria established a priori and were assessed by two independent reviewers; quality assessments of the evidence were performed in accordance with health technology assessment recommendations from the National Institute for Health and Care Excellence. Several types of therapies were included, such as chimeric antigen receptor (CAR) T cell products (lisocabtagene maraleucel, axicabtagene ciloleucel, tisagenlecleucel), novel therapies (selinexor, nivolumab, polatuzumab vedotin, and bendamustine), salvage therapies, and rituximab.

Results The review identified 33 unique studies reporting HRQOL, including 15 economic studies that reported health state utility values, 9 clinical trials, 7 health technology assessment reports, and 1 each of a vignette-based study and a point-in-time survey. Improvements in general and/or lymphoma-specific HRQOL measures were observed with CAR T cell therapy in both the second-line and third-line or later settings. On-treatment utility values for CAR T cell therapies ranged from 0.50 to 0.74. Values for remission/progression-free survival (0.70–0.90) and for disease progression (0.39–0.59) were similar across studies. For novel therapies, utility values were 0.83 for progression-free survival and ranged from 0.39 to 0.71 for disease progression. On-treatment utility values for salvage chemotherapy ranged from 0.63 to 0.67.

Conclusions Overall, the evidence synthesized in this SLR provides a comprehensive understanding of the HRQOL evidence in R/R LBCL. This article identified several sources for utility values in the published literature showing variation in the HRQOL outcomes for patients across a variety of therapeutics. Treatment of R/R LBCL with CAR T cell therapies was associated with improvement in health utility values. Mixed results were found for novel therapies and salvage therapies. More data are needed as new therapies are used in this patient population to inform treatment decision-making.

1 Introduction

Non-Hodgkin lymphoma (NHL) is one of the most common forms of cancer worldwide, with incidence rates in 2020 of 6.9 and 4.8 per 100,000 in males and females, respectively [1]. Diffuse large B cell lymphoma (DLBCL) represents the most common NHL subtype of large B cell lymphoma (LBCL) worldwide [2]. First-line treatment for large B cell lymphoma (LBCL) generally comprises rituximab-containing immunochemotherapy regimens, most commonly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [3, 4]. Standard first-line therapy with immunochemotherapy regimens such as R-CHOP is considered highly effective. Approximately 70% of patients with DLBCL will be event-free at 2 years and have overall survival (OS) equivalent to the general population from that point forward [5].

For those patients with relapsed or refractory (R/R) LBCL (~30% with DLBCL), second-line therapy generally

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Key Points for Decision Makers

While the systematic literature review (SLR) assessments showed a wide range of reporting parameters and conventions, chimeric antigen receptor (CAR) T cell therapies, novel agents, rituximab, and a variety of salvage chemotherapies were collated. The most consistent and broadest range of health-related quality of life (HRQOL) outcomes and health utility values were for CAR T cell therapies, which showed overall improvements/benefits.

The perpetually evolving treatment landscape requires periodic consolidation of HRQOL and health utility value data to inform treatment decision-making. Consistency in reporting of these studies would be more useful for SLRs such as this one.

entails a rituximab-based multiagent regimen to induce a complete response, followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT) with or without involved site radiation therapy [3, 4]. Recently, chimeric antigen receptor (CAR) T cell therapies have been shown to be new assets in the second-line or later treatment armamentarium [6, 7]. The third-line or later setting utilizes a variety of small-molecule (conventional), cellular, and targeted molecular therapies [3, 8, 9].

Health-related quality of life (HRQOL) instruments are useful in monitoring patients' experiences of both disease and treatment. Patients with LBCL have a decreased HRQOL [10, 11]. The impact of treatment on HRQOL varies by therapeutic modality and has been highlighted as an important factor to consider in treatment decision-making in LBCL [12, 13]. In the R/R treatment setting, patients with LBCL may have cumulative toxicities from prior therapies [14], which may also contribute to HRQOL burden.

The HRQOL instruments used in LBCL are varied, and include the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the health state index score and EuroQol visual analog scale (VAS) from the EuroQol 5-dimension 5-level (EQ-5D-5L), the Functional Assessment of Cancer Therapy-General (FACT-G), the FACT lymphoma (FACT-Lym) subscale, and the 36-item Short Form Health Survey (SF-36) [10, 11, 15–20].

Health state utility measures of HRQOL are patient derived using multi-attribute, preference-based values that indicate the effect on the patient's overall health status. In clinical trials, utility measures summarize both positive and negative effects of an intervention, on a scale of 0 (dead) to 1 (full health). These measures allow for comparison of overall patient outcomes across different diseases, and for comparison between various health care interventions. Utility values are used by decision-makers to determine reimbursement, which may have an impact on the availability of certain treatments [21].

A number of new agents, combinations, and regimens are currently under investigation for the treatment of R/R LBCL [4, 5, 19, 22–29]. In this ever-expanding treatment landscape, there is need for consolidated HRQOL evidence in R/R LBCL to help patients and physicians make treatment decisions. The current systematic literature review (SLR) was performed to understand the HRQOL associated with treatments in R/R LBCL and identify associated health utility values.

2 Methods

2.1 Study Design and Search Process

This unregistered SLR was designed, conducted, and reported using best practices in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement [30, 31]. The initial search was conducted on 5 February 2021, and updated on 2 May 2022. The search and modifications to the protocol aligned with Population, Intervention, Comparator, Outcome, Study design (PICOS) criteria [32] to investigate the research question. The database search was developed in Ovid MEDLINE (Supplementary Table S1) by an experienced information specialist and underwent a Peer Review of Electronic Search Strategies (PRESS) [33] analysis by a second information specialist. The search syntax was then adapted in Ovid across Embase, the *Cochrane Database of Systematic Reviews*, the Centre for Reviews and Dissemination Health Technology Assessment (HTA) database, and the National Health Service Economic Evaluation Database. Single searches of conferences and gray literature sources were also conducted (Supplementary Table S2). Protocol requests can be requested using the following website: https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

2.2 Eligibility Criteria

Studies were screened based on PICOS criteria established a priori (Table 1) and were assessed by two independent reviewers. Study screening of the database search

was conducted in the following two stages in DistillerSR (Evidence Partners Inc., Ottawa, ON, Canada): (1) review of titles and abstracts and (2) review of full-text articles. Exclusion reasons were recorded in detail during the full-text screening stage. Searches for gray literature including conference abstracts and hand searches of bibliographies of published SLRs were conducted by a single reviewer and verified by a second reviewer. Conflicts for both the PICOS and gray literature reviews were resolved by consensus through discussion or a third reviewer.

Randomized and nonrandomized studies and economic evaluations reporting health state utility values or HRQOL measures were eligible. Assessments from HTA agencies with full reviewer's reports available from the National Institute for Health and Care Excellence (NICE; UK), Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Benefits Advisory Committee (PBAC, Australia), and Scottish Medicines Consortium (SMC) were also eligible to ensure the most complete set of analysis results supporting HTA recommendations were captured. Studies were not limited by sample size.

2.3 Data Extraction and Quality Assessment

Data extraction was performed using a standardized form implemented in Microsoft Excel. For each study, data were extracted by one reviewer and verified by a second independent reviewer.

The quality of published trials was assessed using a NICE-recommended checklist [34] for appraising review articles to ensure search and resulting analyses are unbiased and of sufficient quality to guide policy and practice. Quality assessments were conducted by a single reviewer and validated by a second reviewer. Conflicts were resolved by a third reviewer when the two reviewers did not reach an agreement. Studies were not excluded on the basis of the quality assessment. Quality assessments for the risk of bias are summarized in Supplementary Table S3.

3 Results

3.1 SLR Search Results

The initial SLR identified 1072 records and an additional 84 when updated (Fig. 1 and Supplementary Fig. S1). The initial gray literature search identified 8244 additional records for consideration and 6476 more when updated. After removing duplicates, screening, and searching reference lists and Supplementary Material, a total of 33 unique studies reporting HRQOL outcomes were included in the qualitative synthesis. Studies included in this analysis that reported HRQOL measures or health state utility values are summarized in Supplementary Table S4.

3.2 HRQOL

Seven studies were identified that assessed and reported disease-specific HRQOL measures (Table 2).

3.2.1 CAR T Cell Therapies

Three studies reported HRQOL data in patients with LBCL treated with CAR T cell therapies, including lisocabtagene maraleucel (liso-cel; $n = 186$ [17] and 184 [18] evaluable patients) and tisagenlecleucel ($n = 108$ [19]). In the phase 1, seamless design, single-arm trial of liso-cel (TRANSCEND NHL 001 [17]), the EORTC QLQ-C30 global health status instrument was used to assess HRQOL in patients with third-line or later LBCL who received liso-cel [35–37]. Baseline HRQOL scores improved by + 17.5 points at the month-12 follow-up after treatment.

The TRANSFORM trial [18] used the FACT-Lym subscale and EORTC QLQ-C30 to evaluate HRQOL in patients with LBCL treated with liso-cel or standard of care (SOC; platinum-based immunochemotherapy followed by carmustine, etoposide, cytarabine, and melphalan, and autologous HSCT in responders) as second-line therapy [18]. Mean change at day 126 (2 months after treatment) from baseline was reported. Improvements in mean scores were observed for both instruments for liso-cel and SOC. For liso–cel–treated patients, the mean [95% confidence interval (CI)] FACT-Lym increase was + 1.48 (0.30−3.26) and the mean EORTC QLQ-C30 increase was + 3.08 (− 1.83 to 7.99); for SOC-treated patients, the mean (95% CI) FACT-Lym increase was + 1.63 (0.41−3.68) and the mean (95% CI) EORTC QLQ-C30 increase was + 0.04 (− 5.24 to 5.31).

In the JULIET trial, change in HRQOL in patients with LBCL after treatment with tisagenlecleucel in the third-line or later setting was measured using the FACT-G, FACT-Lym, and SF-36 instruments [19]. HRQOL improved from baseline to 18-month follow-up across all instrument subscales, with mean change scores ranging from + 3.1 to + 13.1 points in the FACT instrument scales and + 2.3 to + 4.3 for the SF-36 subscales.

3.2.2 Novel Therapies

The phase 2 single-arm SADAL trial (selinexor) assessed HRQOL in responders and nonresponders using the FACT-G treatment satisfaction, FACT-Lym, and FACT-Lym Trial Outcome Index (TOI) [38]. Outcomes were assessed at baseline, treatment cycles 2−7, and the end of treatment. All patients reported decreased HRQOL at last follow-up, with

Table 1 PICOS criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients Relapsed or refractory Secondary CNS lymphoma One of the following NHL subtypes[a]: DLBCL NOS DLBCL tFL DLBCL tiNHLs, including tCLL (Richter's syndrome/transformation) tMZL tPCMZL tPCFCL Hairy cell leukemia Waldenström macroglobulinemia Other low-grade/indolent lymphomas FL3B, or HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations with DLBCL histology PMBCL	Patients aged < 18 years All other lymphoma types Primary CNS lymphoma
Intervention/comparators	Therapies Single-agent or multiagent chemotherapy Chemoimmunotherapy Single-agent or multiagent immunotherapy CAR T cell therapies Treatment concepts Allogeneic HSCT Autologous HSCT Salvage therapy Best supportive care Placebo No comparator	Those not listed
Time frame	Studies published in 2003 or later Conference abstracts (2016 onward in database searches; 2018 onward identified in hand searches)	Articles published before 2003 Abstracts published before 2018 identified in hand searches
HRQOL outcomes	Direct utility values EQ-5D-5L EQ-5D-3L HUI mark 2, HUI2 or mark 3, HUI3 QWB index AQOL 15D SF-6D Scores that can be mapped to utility values FACIT-Fatigue Scale EORTC QLQ-C30 FACT FACT-Lym SF-36	Those not listed
Study design	Published clinical trials, observational studies, registries, systematic reviews and meta-analyses, vignette studies Economic evaluations: cost-effectiveness, cost-utility, cost-benefit, cost-minimization, cost-consequence, microcosting analyses Assessment from HTA agencies where full reviewer's reports are available, specifically CADTH, NICE, PBAC, and SMC	Budget impact, burden of illness, and cost of illness studies Assessments from HTA agencies without full reviewer's reports Animal studies, in vitro studies, case reports, expert opinion articles, commentaries, letters

15D 15-dimensional instrument; *AQOL* Assessment of Quality of Life; *CADTH* Canadian Agency for Drugs and Technologies in Health; *CAR* chimeric antigen receptor; *CNS* central nervous system; *DLBCL* diffuse large B-cell lymphoma; *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; *EQ-5D-3L* EuroQol 5-dimensional, 3-level; *EQ-5D-5L* EuroQol 5-dimensional, 5-level; *FACIT* Functional Assessment of Chronic Illness Therapy; *FACT* Functional Assessment of Cancer Therapy; *FACT-Lym* Functional Assessment of Cancer Therapy—Lymphoma; *FL3B* follicular lymphoma grade 3B; *HGBCL* high-grade B cell lymphoma; *HSCT* hematopoietic stem cell transplantation; *HTA* health technology assessment; *HUI* health utility index; *NHL* non-Hodgkin lymphoma; *NICE* National Institute for Health and Care Excellence; *NOS* not otherwise specified; *PBAC* Pharmaceutical Benefits Advisory Committee; *PICOS* Population, Intervention, Comparator, Outcome, Study design; *PMBCL* primary mediastinal B cell lymphoma; *QWB* Quality of Well-Being; *SF-6D* Short Form 6 Dimensions; *SF-36* 36-item Short Form; *SMC* Scottish Medicines Consortium; *tCLL* transformed chronic lymphocytic leukemia; *tFL* transformed follicular lymphoma; *tiNHL* transformed indolent non-Hodgkin lymphoma; *tMZL* transformed marginal zone lymphoma; *tPCFCL* transformed primary cutaneous follicle center lymphoma; *tPCMZL* transformed primary cutaneous marginal zone lymphoma

[a]Subtypes reflect those eligible for inclusion in the TRANSFORM trial [66]

responders reporting mean change scores from baseline of − 9.9 to − 6, and nonresponders reporting mean change scores of − 9.2 to − 15.7.

In the phase 3 ORCHARRD trial of ofatumumab plus dexamethasone, cytarabine, and cisplatin (DHAP) chemotherapy versus rituximab plus DHAP (R-DHAP) therapy for second-line LBCL, HRQOL was assessed using the FACT-G and FACT-Lym TOI instruments [39]. In patients treated with ofatumumab, the mean [standard error (SE)] FACT-G total score and FACT-Lym TOI decrease was − 2.561 (0.7671) and − 2.028 (0.9196), respectively. In patients treated with R-DHAP, the mean (SE) FACT-G total score and FACT-Lym TOI decrease was − 2.591 (0.7696) and − 3.156 (0.9204), respectively.

3.2.3 Salvage Therapies

One phase 1/2, single-arm trial evaluating the clinical efficacy of rituximab plus cyclophosphamide, etoposide, and prednisone (R-CVEP) used the FACT-G and FACT-Lym instruments to measure HRQOL [40]. HRQOL improved from baseline to 12-month follow-up across all scales, with a mean change in FACT-G total score of + 11.72, FACT-Lym total score of + 18.61, and FACT-Lym TOI of + 12.29.

3.2.4 EORTC QLQ-C30 by Line of Therapy

One identified study reported HRQOL by line of therapy in a real-world setting for patients with DLBCL via a self-completed point-in-time survey using the EORTC QLQ-C30. The reported EORTC QLQ-C30 global health status

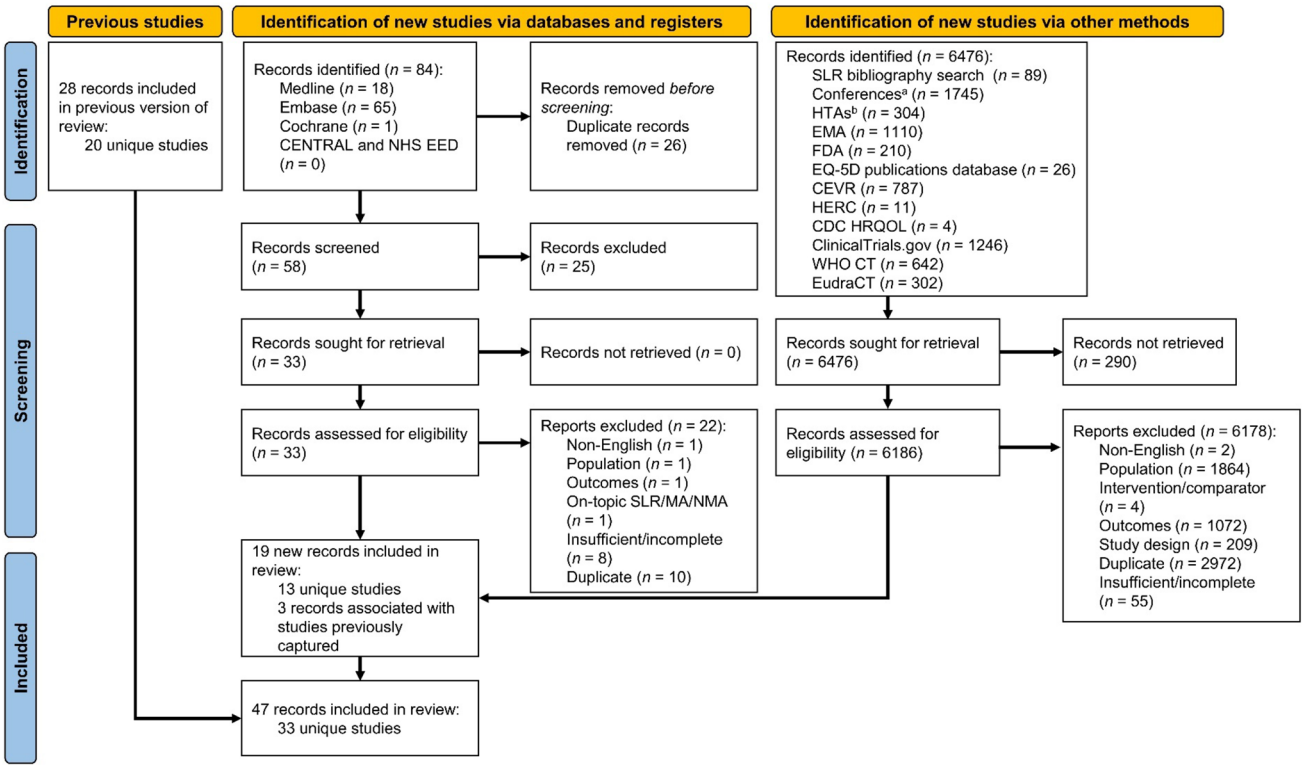

Fig. 1 PRISMA flow diagram. *CDC* Centers for Disease Control and Prevention; *CEVR* Center for Evaluation of Value and Risk in Health; *EMA* European Medicines Agency; *Embase* Excerpta Medica dataBASE; *EQ-5D* EuroQol 5-dimensional; *EudraCT* European Union Drug Regulating Authorities Clinical Trials Database; *FDA* United States Food and Drug Administration; *HERC* Health Economics Research Centre; *HRQOL* health-related quality of life; *HTA* health technology assessment; *MA* meta-analysis; *MEDLINE* Medical Literature Analysis and Retrieval System Online; *NMA* network meta-analysis; *NHS EED* National Health Service Economic Evaluation Database; *PRISMA* Preferred Reporting Items for Systematic reviews and Meta-Analyses; *SLR* systematic literature review; *WHO CT* World Health Organization Clinical Trials. [a]Conferences searched included American Association for Cancer Research (n = 426), American Society of Clinical Oncology (n = 313), American Society of Hematology (n = 745), European Hematology Association (n = 178), European Society for Medical Oncology (n = 33), International Society for Pharmacoeconomics and Outcomes Research (n = 50). [b]Sources of HTAs searched included Canadian Agency for Drugs and Technologies in Health (n = 22), Health Technology Assessment International (n = 0), Institut National d'Excellence en Santé et en Services Sociaux (n = 64), National Institute for Health and Care Excellence (n = 73), Pharmaceutical Benefits Advisory Committee (n = 13), and Scottish Medicines Consortium (n = 132)

Table 2 Overview of included studies on HRQOL measures

Region	Study Author year	Study design/ study type	Patient population	Treatment	Follow-up times assessed	Assessment method	Scale	Baseline mean (SD)	Mean change at last follow-up (SD)
HRQOL measures mappable to direct utility values									
FACT-G									
Global	JULIET Maziarz 2020 [19] Tam 2019 [67] Maziarz 2017 [68]	Phase 2 single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Tisagenlecleucel	Baseline 3 months 6 months 12 months 18 months	FACT-G TS	0 to 108 (higher scores reflecting better health)	77.4 (16.1)	+ 10 (11.1)
Global	ORCHARRD ClinicalTrials.gov [39]	Phase 3 trial	Adult patients with R/R DLBCL	Ofatumumab + DHAP R-DHAP	Baseline End of treatment	FACT-G TS	0 to 108 (higher scores reflecting better health)	NR NR	− 2.561 (SE, 0.7671) − 2.591 (SE, 0.7696)
Global	SADAL Shah 2021 [38] Casasnovas 2020 [69]	Phase 2b single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Selinexor	Baseline Cycle 2 Cycle 3 Cycle 4 Cycle 5 Cycle 6 Cycle 7 End of treatment	FACT-G	0 to 116 (higher scores reflecting better health)	Responders: 72.6 (95% CI, 70.9, 74.3) Nonresponders: 72.9 (95% CI, 71.3, 74.4)	Responders: − 6.0 (95% CI, − 9.2, − 2.8) Nonresponders: − 9.2 (NR)
US	NCT00667615 Straus 2015 [40]	Phase 1/2 single-arm trial	Patients with R/R DLBCL, aged 60 years or older, not eligible for autologous HSCT	R-CVEP	Baseline Cycle 1 Cycle 2 Cycle 3 Cycle 4 Cycle 5 Cycle 6 3 months 6 months 9 months 12 months	FACT-G TS	0 to 108 (higher scores reflecting better health)	75.48 (17.44)	+ 11.72 (15.14)
FACT-Lym									

Table 2 (continued)

Region	Study Author year	Study design/ study type	Patient population	Treatment	Follow-up times assessed	Assessment method	Scale	Baseline mean (SD)	Mean change at last follow-up (SD)
Global	JULIET Maziarz 2020 [19] Tam 2019 [67] Maziarz 2017 [68]	Phase 2 single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Tisagenlecleucel	Baseline 3 months 6 months 12 months 18 months	FACT-Lym TS[a]	0 to 168 (higher scores reflecting better health)	121.2 (24.0)	+ 13.1 (16.1)
						FACT-Lym TOI	0 to 116 (higher scores reflecting better health)	82.0 (19.0)	+ 9.2 (13.6)
						FACT-Lym subscale	0 to 60 (higher scores reflecting better health)	44.4 (9.1)	+ 3.1 (6.6)
Global	ORCHARRD ClinicalTrials.gov [39]	Phase 3 trial	Adult patients with R/R DLBCL	Ofatumumab + DHAP R-DHAP	Baseline End of treatment	FACT-Lym TOI	0 to 116 (higher scores reflecting better health)	NR	− 2.028 (SE, 0.9196) − 3.156 (SE, 0.9204)
Global	SADAL Shah 2021 [38] Casasnovas 2020 [69]	Phase 2b single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Selinexor	Baseline Cycle 2 Cycle 3 Cycle 4 Cycle 5 Cycle 6 Cycle 7 End of treatment	FACT-Lym TS	0 to 168 (higher scores reflecting better health)	Responders: 116.7 (95% CI, 114.2, 119.2) Nonresponders: 117.1 (95% CI, 114.9, 119.4)	Responders: − 9.9 (95% CI, − 15.5, − 4.3) Nonresponders: − 15.7 (NR)
						FACT-Lym TOI	0 to 116 (higher scores reflecting better health)	Responders: 77.4 (95% CI, 75.3, 79.4) Nonresponders: 79.2 (95% CI, 77.3, 81.0)	Responders: − 8.6 (95% CI, − 13.0, − 4.3) Nonresponders: − 13.5 (NR)

Table 2 (continued)

Region	Study Author year	Study design/ study type	Patient population	Treatment	Follow-up times assessed	Assessment method	Scale	Baseline mean (SD)	Mean change at last follow-up (SD)
US	NCT00667615 Straus 2015 [40]	Phase 1/2 single-arm trial	Patients with R/R DLBCL, aged 60 years or older, not eligible for autologous HSCT	R-CVEP	Baseline Cycle 1 Cycle 2 Cycle 3 Cycle 4 Cycle 5 Cycle 6 3 months 6 months 9 months 12 months	FACT-Lym TS[b]	0 to 168 (higher scores reflecting better health)	117.1 (26.29)	+ 18.61 (19.89)
						FACT-Lym TOI	0 to 116 (higher scores reflecting better health)	76 (21.48)	+ 12.29 (19.49)
NR	TRANSFORM Abramson 2021 [18]	Phase 3 RCT	Adults aged ≤ 75 years with R/R LBCL ≤ 12 months after 1L therapy	Liso-cel SOC (salvage chemotherapy + BEAM + autologous HSCT)	Baseline 1 month 2 months 3 months 6 months End of study or 36 months	FACT-Lym subscale	0 to 60 (higher scores reflecting better health)	NR NR	+ 1.48 (95% CI, − 0.30, 3.26)[c] + 1.63 (95% CI, − 0.41, 3.68)
EORTC QLQ-C30									
UK, US, France, Germany, Italy, Spain	Ma 2021 [41]	Point in time survey	Adult patients with DLBCL in 2 or 3 + lines of therapy	NR	NR	EORTC QLQ-C30 global health status[d]	0 to 100 (higher scores reflecting better health)	2L: 55.48 (18.02) 3L +: 49.93 (21.07)	NR
US	TRANSCEND NHL 001 Patrick 2021 [17] Patrick 2020 [37] Patrick 2019 [35] Patrick 2019 [36]	Phase 1 single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Liso-cel	Baseline 1 month 2 months 3 months 6 months 9 months 12 months 18 months	EORTC QLQ-C30 global health status[c]	0 to 100 (higher scores reflecting better health)	62.3 (20.3)	19.7 (25.6)
NR	TRANSFORM Abramson 2021 [18]	Phase 3 single-arm trial	Adults aged ≤ 75 years with R/R LBCL ≤ 12 months after 1L therapy	Liso-cel SOC (salvage chemotherapy + BEAM + autologous HSCT)	Baseline 1 month 2 months 3 months 6 months End of study or 36 months	EORTC QLQ-C30 global health status[d]	0 to 100 (higher scores reflecting better health)	NR NR	+ 3.08 (95% CI, − 1.83, 7.99) + 0.04 (95% CI, − 5.24, 5.31)[c]

Table 2 (continued)

Region	Study Author year	Study design/ study type	Patient population	Treatment	Follow-up times assessed	Assessment method	Scale	Baseline mean (SD)	Mean change at last follow-up (SD)
SF-36									
Global	JULIET Maziarz 2020 [19] Tam 2019 [67] Maziarz 2017 [68]	Phase 2 single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Tisagenlecleucel	Baseline 3 months 6 months 12 months 18 months	SF-36 PCS	0 to 100 (higher scores reflecting better health)	44.3 (9.17)	+ 4.3 (10.6)
						SF-36 MCS	0 to 100 (higher scores reflecting better health)	48.1 (10.5)	+ 2.3 (9.8)

1L first line; *2L* second line; *3L+* third line or later; *BEAM* carmustine, etoposide, cytarabine, and melphalan; *CI* confidence interval; *DHAP* dexamethasone, cytarabine, and cisplatin; *DLBCL* diffuse large B cell lymphoma; *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; *FACT-G* Functional Assessment of Cancer Therapy—General; *FACT-Lym* Functional Assessment of Cancer Therapy—Lymphoma; *FACT-Lym TOI* Functional Assessment of Cancer Therapy—Lymphoma Trial Outcomes Index; *HRQOL* health-related quality of life; *HSCT* hematopoietic stem cell transplantation; *LBCL* large B cell lymphoma; *liso-cel* lisocabtagene maraleucel; *MCS* mental component summary; *NR* not reported; *PCS* physical component summary; *RCT* randomized controlled trial; *R-CVEP* rituximab plus cyclophosphamide, etoposide, and prednisone; *R-DHAP* rituximab plus dexamethasone, cytarabine, and cisplatin; *R/R* relapsed or refractory; *SD* standard deviation; *SE* standard error; *SF-36* 36-item Short Form; *SOC* standard of care; *TS* total score; *UK* United Kingdom; *US* United States

[a]FACT-Lym TS is composed of the FACT-G score (0−108) and FACT-Lym subscale (0−60)

[b]Utility values can occasionally be below zero, reflecting a health state less preferable than dead

[c]Study also reported select components of the EORTC QLQ-C30 symptomatic and functional domains

[d]Reported value is overall least squares mean changes from baseline to 2 months after liso-cel therapy

score was higher for patients on second-line therapies (55.48 [18.02]) than for those on third-line and beyond therapies (49.93 [21.07]) [41].

3.3 Utilities

Six studies were identified that assessed and reported health state utility values (Table 3).

3.3.1 CAR T Cell Therapies

Three studies reported HRQOL data in patients with LBCL treated with CAR T cell therapies as follows: liso-cel (TRANSCEND NHL 001; $n = 186$ evaluable patients [17]), axicabtagene ciloleucel (axi-cel; ZUMA-1; $n = 34$ [42]), and a product-agnostic vignette-based time tradeoff study [43, 44]). In TRANSCEND NHL 001, the health utility impact of liso-cel was evaluated in eligible patients with DLBCL in the third-line or later setting using the validated EQ-5D-5L questionnaire [17, 35–37]. The questionnaire includes the EQ-5D-5L descriptive system and EQ-VAS. Health utilities were assessed at baseline and months 1, 2, 3, 6, 9, 12, and 18 after infusion. At baseline, the mean [standard deviation (SD)] EQ-5D-5L health state score was 0.817 (0.120). This decreased slightly at month 1 (− 0.023) and then increased from months 2 to 12 (+ 0.020 to + 0.031). At month 18, the increase from baseline in the EQ-5D-5L index score was + 0.061 (0.013). The mean (SD) score for EQ-5D-5L VAS at baseline was 68.3 (19.5), and the increase from baseline was + 10.4 (5.4) at month 18.

A phase 2 ZUMA-1 safety management study ad hoc analysis investigated the impact of axi-cel treatment on health utility patients with R/R LBCL in the third-line or later setting, as measured by the EQ-5D-5L [42]. Health utilities were assessed at screening, week 4, and months 3 and 6 after infusion. Mean (SD) EQ-5D-5L score at baseline was 0.80 (0.17). Scores at week 4 decreased slightly [0.74 (0.15); − 0.06] and then increased by month 3 [0.80 (0.13); + 0.00] and month 6 [0.82 (0.21); + 0.02]. Mean (SD) utility values by health state were 0.80 (0.14) for progression-free disease and 0.72 (0.17) for progressed disease. A disutility of 0.05 (SE, 0.04) was observed at 4 weeks, and the authors noted this was associated with the timing of CAR T cell–related adverse events (AE).

In a vignette-based time tradeoff study [43, 44], adults from the general population in the UK were surveyed to estimate the health utility impact of all-grade cytokine release syndrome (CRS) and neurological events (NE) related to CAR T cell treatment for R/R LBCL. The EQ-5D-5L was self-administered, and participants were also asked to value the following six health states: one state describing CAR T cell therapy for LBCL with no AEs, three states describing CAR T cell therapy for LBCL with varying grades of CRS, and two states describing CAR T cell therapy for LBCL with varying grades of NEs. A total of 218 participants completed the interview. The mean (SD) EQ-5D-5L index score was 0.86 (0.17) and the mean (SD) EQ-5D-5L VAS score was 82.15 (13.54) for the general population. Among the six health state vignettes valued by the general population respondents, the highest mean utility was for the health state representing CAR T cell therapy with no AEs. Disutilities per AE included grade 1 CRS (− 0.01), grade 1/2 NEs (− 0.04), grade 2 CRS (− 0.05), grade 3/4 NEs (− 0.18), and grade 3/4 CRS (− 0.23).

3.3.2 Novel Therapies

The phase 2 single-arm SADAL trial evaluated the health utility impact of selinexor in the third-line or later setting in eligible patients with DLBCL using the validated EQ-5D-5L questionnaire [38]. Health utilities were assessed in responders and nonresponders at baseline and at cycles 2−7. At baseline ($n = 89$ evaluable patients), the mean (95% CI) EQ-5D health state score was 0.789 (0.767−0.811) for responders and 0.801 (0.781−0.822) for nonresponders. Responders reported a mean change from baseline of − 0.010 at last follow-up, whereas nonresponders reported a mean change from baseline of − 0.274.

In the phase 1/2 CheckMate 436 trial, HRQOL was reported as an exploratory endpoint in patients with primary mediastinal B cell lymphoma treated with nivolumab combined with brentuximab vedotin in the third-line or later setting using the EQ-5D-3L [45]. HRQOL was reported at baseline, cycle 5, and for the first follow-up visit. The study reported the proportion of patients experiencing "some problems" or "extreme problems" for each dimension but did not map the results to preference-based health state utilities. The percentage of patients experiencing "some problems" with activity and pain appeared to decrease over time (− 18% and − 50%, respectively), and no clear pattern could be seen for the remaining dimensions.

The impact of naratuximab emtansine and rituximab in patients with R/R DLBCL was evaluated in a phase 2 single-arm trial using the FACT-Lym questionnaire mapped to EQ-5D index values [46]. At baseline, the mean estimated EQ-5D index score was 0.78 for responders and 0.73 for nonresponders. At the end of treatment, mean (difference) index scores were 0.77 (− 0.01) for responders and 0.67 (− 0.06) for nonresponders.

3.4 Health State Utility Values Reported in Economic Studies and HTA Submissions

A total of 15 economic studies and seven HTA reports were identified that reported health state utility values used to

Table 3 Overview of included studies on health statue utility values

Region	Study Author year	Study design/study type	Patient population	Treatment	Follow-up times assessed	Utility assessment method	Scale	Baseline mean (SD)	Mean change at last follow-up (SD)
Utilities									
EQ-5D									
Global	CheckMate 436 Zinzani 2019 [45]	Phase 1/2 single-arm study	Adult patients with R/R PMBCL	Nivolumab + brentuximab vedotin	Baseline Cycle 5 Follow-up 1	EQ-5D-3L mobility	0 (no problems) to 3 (extreme problems)	Some problems: 14% Extreme problems: 0	Some problems: 21% Extreme problems: 0
						EQ-5D-3L self-care	0 (no problems) to 3 (extreme problems)	Some problems: 11% Extreme problems: 0	Some problems: 14% Extreme problems: 0
						EQ-5D-3L activity	0 (no problems) to 3 (extreme problems)	Some problems: 39% Extreme problems: 0	Some problems: 21% Extreme problems: 0
						EQ-5D-3L pain	0 (no problems) to 3 (extreme problems)	Some problems: 71% Extreme problems: 7%	Some problems: 21% Extreme problems: 7%
						EQ-5D-3L anxiety	0 (no problems) to 3 (extreme problems)	Some problems: 46% Extreme problems: 0	Some problems: 57% Extreme problems: 0
Global	SADAL Shah 2021 [38] Casasnovas 2020 [69]	Phase 2b single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Selinexor	Baseline Cycle 2 Cycle 3 Cycle 4 Cycle 5 Cycle 6 Cycle 7	EQ-5D-5L health index score	0 (dead) to 1 (perfect health)	Responders: 0.789 (95% CI, 0.767, 0.811) Nonresponders: 0.801 (95% CI, 0.781, 0.822)	Responders: − 0.010 (95% CI, − 0.15, − 0.05) Nonresponders: − 0.274 (NR)
Global	ZUMA-1 Lin 2019 [42] ClinicalTrials.gov [70]	Phase 2 single-arm trial	Adult patients with 3L + DLBCL of therapy (Cohorts 3−6)	Axi-cel	Baseline Week 4 Month 3 Month 6	EQ-5D-5L visual analog scale	0 to 100 (higher scores reflecting better health)	Cohort 3: 71.2 (21.3) Cohort 4: 69.5 (18.8) Cohort 5: 66.7 (20.7) Cohort 6: 70.9 (17.0)	Cohort 3: + 5.9[a] Cohort 4: + 15.6[a] Cohort 5: + 10.4[a] Cohort 6: + 8.9[a]
			Adult patients with 3L + LBCL (safety management study)		Baseline 1 month 2 months 3 months 6 months	EQ-5D-5L health index score	0 (dead) to 1 (perfect health)	0.80 (0.17)	0.82 (0.21)
US	TRANSCEND NHL 001 Patrick 2021 [17] Patrick 2020 [37] Patrick 2019 [35] Patrick 2019 [36]	Phase 1 single-arm trial	Adult patients with R/R DLBCL with 2 + prior lines of therapy	Liso-cel	Baseline 1 month 2 months 3 months 6 months 9 months 12 months 18 months	EQ-5D-5L health index score	0 (dead) to 1 (perfect health)[a]	0.817 (0.120)	+ 0.061[b] (0.013)
						EQ-5D-5L visual analog scale	0 to 100 (higher scores reflecting better health)	68.3 (19.5)	+ 10.4 (5.4)
NR	Orfanos 2022 [46]	Phase 2 single-arm trial	2L and heavily pretreated patients with R/R DLBCL	Naratuximab emtansine + rituximab	Baseline End of therapy	EQ-5D (unspecified)	0 (dead) to 1 (perfect health)	Responders: 0.78 (NR) Nonresponders: 0.73 (NR)	Responders: 0.77 (NR) Nonresponders: 0.67 (NR)

Table 3 (continued)

Region	Study Author year	Study design/study type	Patient population	Treatment	Follow-up times assessed	Utility assessment method	Scale	Baseline mean (SD)	Mean change at last follow-up (SD)
UK	Howell 2022 [44] Howell 2020 [43]	Vignette-based study	General adult population in UK	Hypothetical CAR T cell therapy pathway	NA	EQ-5D-5L health index score	0 (dead) to 1 (perfect health)[c]	0.86 (0.17)	NR
						EQ-5D-5L visual analog scale	0 to 100 (higher scores reflecting better health)	82.15 (13.54)	NR
TTO									
UK	Howell 2022 [44] Howell 2020 [43]	Vignette-based study	General adult population in UK	Hypothetical CAR T cell therapy pathway	NA	TTO (1-year time horizon)	0 (dead) to 1 (perfect health)[c]	NR (results are disutilities of a hypothetical treatment pathway [i.e., no baseline])	CAR T cell therapy for LBCL with grade 1 CRS: − 0.01 (0.04)[d] CAR T cell therapy for LBCL with grade 2 CRS: − 0.05 (0.09)[d] CAR T cell therapy for LBCL with grade 3/4 CRS: − 0.23 (0.24)[d] CAR T cell therapy for LBCL with grade 1/2 NEs: − 0.04 (0.07)[d] CAR T cell therapy with grade 3/4 NEs: − 0.18 (0.22)[d]

2L second line; *3L+* third line or later; *AE* adverse event; *axi-cel* axicabtagene ciloleucel; *CAR* chimeric antigen receptor; *CI* confidence interval; *CRS* cytokine release syndrome; *DLBCL* diffuse large B cell lymphoma; *EQ-5D-3L* EuroQol 5-dimensional, 3-level; *EQ-5D-5L* EuroQol 5-dimensional 5-level; *LBCL* large B cell lymphoma; *liso-cel* lisocabtagene maraleucel; *NA* not available; *NE* neurological event; *NR* not reported; *PMBCL* primary mediastinal large B cell lymphoma; *R/R* relapsed or refractory; *SD* standard deviation; *TTO* time tradeoff; *UK* United Kingdom; *US* United States

[a]EQ-5D visual analog scale values are calculated using the 6-month end score

[b]Mean change was calculated based on baseline and follow-up values

[c]Utility values can occasionally be below zero, reflecting a health state less preferable than dead

[d]Values represent the difference between the utility of the health state without an AE (i.e., base LBCL health state) and with an AE

Table 4 Overview of economic studies reporting health state utility values

Author, year	Region	Study type	Patient population	Treatment	Utility values on-treatment	Utility values in remission	Utility values for disease progression
Li 2022 [54]	China	CUA	Adult patients with R/R DLBCL with ≥ 2 prior lines of systemic therapies	Axi-cel Salvage chemotherapy	Disutility of chemotherapy: − 0.42[a]	0.83	0.39
Wakase 2021 [55]	Japan	CUA	Adult patients with CD19-positive R/R DLBCL who are ineligible for, or relapsed after, autologous HSCT	Tisagenlecleucel Salvage chemotherapy	− 0.15; 28 days[b] − 0.15; 62 days[b]	0.83	0.39
Cher 2020 [53]	Singapore	CUA	Adult patients with R/R DLBCL from JULIET trial and CORAL extension study	Tisagenlecleucel Salvage chemotherapy	Disutility: − 0.15[c] Disutility: − 0.15[c]	0.7	0.59
Wang 2021 [58]	Singapore	CUA	Adult patients with R/R DLBCL with ≥ 2 prior lines of systemic therapies	Tisagenlecleucel Salvage chemotherapy	Disutility: − 0.15[d] Disutility: − 0.15[d]	0.90 (SE, 0.01) 0.90 (SE, 0.01)	0.82 (SE, 0.02) 0.82 (SE, 0.02)
Bastos-Oreiro 2022 [71]	Spain	CUA	Adult patients with R/R DLBCL with ≥ 2 prior lines of systemic therapies	Axi-cel Tisagenlecleucel	Month 1: 0.740	≤ 12 months: 0.782 > 12 months: 0.820	0.39
Muszbek 2016 [62]	UK	CUA	Patients with R/R aggressive NHL receiving third- or fourth-line treatment	Pixantrone Current clinical practice	Grade 2 AE disutility: 0.0075 Grade 3/4 AE disutility: 0.0078 Grade 2 AE disutility: 0.0066 Grade 3/4 AE disutility: 0.0073	Preprogression: 0.76 (SE, 0.03)	0.68 (SE, 0.04)
Betts 2020 [61] Betts 2020 [72]	US	CEA	Adult patients with R/R DLBCL based on GO29365 trial	Pola-BR BR	NR	0.83	0.71
Liu 2021 [49]	US	CUA	Adult patients with R/R DLBCL with ≥ 2 prior lines of systemic therapies	Axi-cel Tisagenlecleucel	Month 1: 0.740	First 24 months: 0.782 > 24 months since: 0.820	0.39
Lin 2019 [50]	US	CUA	US adults with R/R DLBCL after ≥ 2 lines of therapy or relapsed ≤ 12 months after HSCT	Axi-cel Tisagenlecleucel Chemoimmunotherapy Autologous HSCT	Months 1–2: 0.50 Months 1–2: 0.58 During treatment: 0.63 Months 1–2: 0.43 Month 3 (if in remission): 0.70	0.70 0.70 0.71 0.70	0.45

Table 4 (continued)

Author, year	Region	Study type	Patient population	Treatment	Utility values on-treatment	Utility values in remission	Utility values for disease progression
Oluwole 2022 [48]	US	CUA	US adults with R/R LBCL after ≥ 2 lines of therapy	Axi-cel Liso-cel	First model cycle: 0.740	≤ 24 months since model entry: 0.782 > 24 months since model entry: 0.820	0.390
Roth 2018 [51]	US	CUA	Adult patients with R/R DLBCL based on ZUMA-1 trial	Axi-cel Salvage chemotherapy	0.740 0.673	< 6-month follow-up: 0.782 ≥ 6-month follow-up: 0.823	0.390
Whittington 2019 [56]	US	CUA	Adult patients with R/R B cell lymphoma from ZUMA-1 trial	Axi-cel Chemotherapy HSCT	NR Disutility: − 0.42 Disutility: − 0.57	0.83	0.39
Calamia 2021 [59]	US	CUA	Adult patients with R/R DLBCL who are transplant ineligible based on L-MIND and G029365 trials	Pola-BR Tafasitamab + lenalidomide	AE disutility: − 0.02 AE disutility: − 0.01	PFS: 0.83 PFS adjusted for disutility: 0.82	0.39
Patel 2020 [60]	US	CUA	Adult patients with R/R follicular or DLBCL (mirrored phase 2 cohort from NCT02257567)	Pola-BR BR	Disutility from chemotherapy: − 0.42	0.83	0.39
Qi 2021 [57]	US	CUA	Adults with R/R DLBCL after ≥ 2 lines of therapy	Tisagenlecleucel Salvage chemotherapy	Disutility: − 0.15 (duration: 27.9 days)[e] Disutility: − 0.15 (duration: 72.2 days)[e]	0.83	0.39

AE adverse event; *axi-cel* axicabtagene ciloleucel; *BR* bendamustine and rituximab; *CRS* cytokine release syndrome; *CEA* cost-effectiveness analysis; *CUA* cost-utility analysis; *DLBCL* diffuse large B cell lymphoma; *HSCT* hematopoietic stem cell transplantation; *ICU* intensive care unit; *NHL* non-Hodgkin lymphoma; *NR* not reported; *PFS* progression-free survival; *pola-BR* polatuzumab vedotin, bendamustine, and rituximab; *R/R* relapsed or refractory; *SE* standard error; *UK* United Kingdom; *US* United States

[a]Reports additional disutility value for HSCT (− 0.57)

[b]Reports additional disutility value for subsequent HSCT (− 0.30/year)

[c]Disutilities were also provided for ICU stay for CRS (− 0.7), AEs (− 0.15), and HSCT (− 0.15)

[d]Disutilities were also provided for ICU stay for CRS (− 0.9), ICU stay for non-CRS AEs (− 0.9), and subsequent HSCT (− 0.30/year)

[e]Disutilities were also provided for ICU stay for CRS (− 0.83; duration 8.5 days) and ICU stay for non-CRS AEs (− 0.83; duration 0.9 days) for tisagenlecleucel-infused patient, and subsequent HSCT (− 0.30/year) for both treatments

inform comparative analyses of therapies for patients with R/R LBCL (Table 4). Reporting of utility values varied among HTA reports ($n = 7$), with six reporting values associated with progression-free and progressed states and one reporting disutility values for specified AEs (Table 5). Sources for utility values were typically clinical trials, as well as published literature. Two reports (both from the SMC) reported mapping SF-36 data to EQ-5D.

3.4.1 CAR T Cell Therapies

Eleven studies reported health state utility values used to inform cost-effectiveness models comparing CAR T cell therapies with other CAR T cell therapies (three studies) [47–49] or salvage chemotherapy (eight studies) [50–57] in patients with DLBCL in the third-line or later setting. These studies were conducted from a number of different perspectives, including US payer perspective [50, 51, 56, 57], Spanish National Health Service perspective [47], Singapore health care system perspective [53], Singapore private insurance payer perspective [58], Chinese health care system perspective [54], and Japanese public health care payer perspective [55]. Across these 11 studies, utility values for remission/progression-free survival ranged from 0.70 to 0.90 [50, 58], and values for disease progression ranged from 0.39 to 0.59 [47, 48, 51, 53–57, 59, 60]. Treatment-related utility values for CAR T cell therapies ranged from 0.50 to 0.740 [47, 48, 50, 51]. Disutilities related to treatment and AEs were reported for tisagenlecleucel: two studies [55, 57] reported treatment disutility of − 0.15 over a duration of 28 days, while disutilities related to intensive care unit stays for CRS ranged from − 0.70 to − 0.90 across three studies [53, 57, 58].

3.4.2 Novel Therapies

Among three cost-effectiveness analyses conducted from a US payer perspective that compared polatuzumab vedotin, bendamustine, and rituximab (pola-BR) with BR (two studies) [60, 61] or tafasitamab plus lenalidomide (one study) [59], utility values were 0.83 for progression-free survival [47, 48, 50, 51, 53–55, 57–62] and ranged from 0.39 to 0.71 for disease progression [47, 48, 50, 51, 53–55, 57–62]. AE-related disutility values were − 0.02 for pola-BR and − 0.01 for tafasitamab plus lenalidomide [59].

3.4.3 Salvage Therapies

One study reported health state utility values for pixantrone compared with current clinical practice (vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, and gemcitabine) in patients with aggressive R/R non-Hodgkin lymphoma [62]. Utility values were reported for preprogression (0.76) and progressive disease (0.68). For pixantrone-treated patients, disutilities were reported for grade 2 AEs (− 0.0075) and grade 3/4 AEs (− 0.0078). For patients treated with current clinical practice, disutilities were reported for grade 2 AEs (− 0.0066) and grade 3/4 AEs (− 0.0073).

Treatment-related utility and disutility values were reported for salvage chemotherapy in eight studies [50, 51, 53–58] and for HSCT in five studies [50, 54–56, 58]. On-treatment utility values for salvage chemotherapy ranged from 0.63 to 0.67 [50, 51]. Disutilities for salvage chemotherapy ranged from − 0.42 to − 0.15 [53–55, 57, 58], while reported disutility values for HSCT ranged from − 0.57 to − 0.30 [55, 56].

3.5 Quality Assessment of HRQOL and Utility Evidence

Six studies (five clinical trials and one vignette-based study) were assessed using the NICE quality assessment criteria for health state utility values. The results are summarized in Supplementary Table S2. Overall, sources of potential bias in the six studies centered around study population (e.g., self-selected participants [41]), small sample size [38, 40, 48], and the presence and handling of missing data (e.g., reasons for loss to follow-up not reported [19, 37, 38] or loss to follow-up unaccounted for in analysis [19, 37]).

4 Discussion

Overall, the evidence synthesized in this review provides a comprehensive synthesis of HRQOL and health state utility evidence for treatments of aggressive R/R LBCL. Analyses were identified for CAR T cell therapies; novel agents such as pola-BR, ofatumumab, and selinexor; and salvage therapies. However, studies were heterogeneous in terms of methods and outcomes reported.

All studies reporting health state utility values reported data for the EQ-5D. Treatment of R/R LBCL with CAR T cell therapies liso-cel, axi-cel, and tisagenlecleucel in the third-line or later setting was associated with improvement in EQ-5D utility values from baseline. Similar improvements in general and lymphoma-specific HRQOL measures (i.e., FACT-G, FACT-Lym, SF-36, and EORTC QLQ-C30 scales) were observed with liso-cel in both the second- and third-line or later settings and for tisagenlecleucel in the third-line or later setting. HTAs varied in their recommendations, sometimes for the same product (e.g., pola-BR).

This SLR has several strengths. It was designed, conducted, and reported using best practices in accordance with the *Cochrane Handbook for Systematic Reviews of*

Table 5 Health state utility values included in HTA reports

Region	HTA report (year)	Type of economic evaluation	Patient population	Treatment	Source of utility values	Utility values reported
Australia	PBAC (2018) [73]	CUA	R/R PMBCL	Pembrolizumab Standard of care chemotherapies including ICE, DHAP, or GDP	Keynote—170 trial	Progression-free state: 0.80 Progressed disease: 0.62
Australia	PBAC (2019) [74]	CUA	Patients with R/R DLBCL who have failed prior therapies and are either ineligible for SCT (due to comorbidities, age, or a failed salvage regimen), or who have had disease relapse after HSCT	Pola-BR BR	JULIET trial/tisagenlecleucel NICE report[21]	Progression-free off treatment: 0.83 Progressive disease: 0.71
Canada	CADTH (2019) [75]	CUA	Adult patients with R/R LBCL after ≥ 2 lines of systemic therapy including DLBCL NOS, HGBCL, and DLBCL arising from FL	Tisagenlecleucel	JULIET trial (8 March 2017 data cutoff)	Disutility values: Short-term AEs associated with treatments (except for CRS): − 0.15 CRS-related or non–CRS-related ICU stay: − 0.83
				Salvage chemotherapy (rituximab plus GDP)	SCHOLAR-1 [76]	Disutility values: Short-term AEs associated with treatments: − 0.15
England and Wales	NICE (2020) [77]	CUA	Patients with R/R DLBCL who are ineligible for HSCT	Pola-BR BR	NICE (2019)	Progression-free survival: 0.72 Progressive disease: 0.65
England and Wales	NICE (2019) [78]	CUA	Adult patients with R/R DLBCL after ≥ 2 lines of systemic therapy	Tisagenlecleucel Salvage chemotherapy (GDP)	JULIET trial	Progression-free state: 0.83 Progressed disease: 0.71 AE disutility: 0.15
England and Wales	NICE (2019) [79]	CUA	Adult patients with R/R DLBCL and PMBCL after ≥ 2 lines of systemic therapy	Axi-cel Salvage chemotherapy excluding pixantrone	ZUMA-1 trial	By follow-up: Screening: 0.739 Week 4: 0.675 Month 3: 0.756 Month 6: 0.758 By response: Complete response: 0.743 Partial response: 0.788 Stable disease: 0.636 Progression-free disease: 0.722 Progressed disease: 0.647
England and Wales	NICE (2014) [80]	CUA	Adults with aggressive de novo or transformed NHL relapsed after ≥ 2 chemotherapy regimens, per ITT population of PIX301	Pixantrone Physician's choice	Published literature for patients receiving second- and subsequent-line treatment for renal cell carcinoma	Manufacturer's submission: Preprogression: 0.81 Postprogression: 0.60 Revised model: Preprogression: 0.76 Postprogression: 0.68

AE adverse event; *axi-cel* axicabtagene ciloleucel; *BR* bendamustine and rituximab; *CADTH* Canadian Agency for Drugs and Technologies in Health; *CRS* cytokine release syndrome; *CUA* cost-utility analysis; *DHAP* dexamethasone, cytarabine, and cisplatin; *DLBCL* diffuse large B cell lymphoma; *FL* follicular lymphoma; *GDP* gemcitabine, dexamethasone, and cisplatin; *HGBCL* high-grade B cell lymphoma; *HSCT* hematopoietic stem cell transplantation; *HTA* health technology assessment; *ICE* ifosfamide, carboplatin, and etoposide; *ICU* intensive care unit; *ITT* intent to treat; *LBCL* large B cell lymphoma; *NHL* non-Hodgkin lymphoma; *NICE* National Institute for Health and Care Excellence; *NOS* not otherwise specified; *PBAC* Pharmaceutical Benefits Advisory Committee; *PMBCL* primary mediastinal large B cell lymphoma; *pola-BR* polatuzumab vedotin, bendamustine, and rituximab; *R/R* relapsed or refractory

Interventions and the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement [30, 31]. This includes the use of a prespecified PICOS question design, comprehensive database literature search, supplementary searches of bibliographies and gray literature, standardized approach to study selection and data extraction with screening by two independent reviewers, and a rigorous quality assessment process. It was designed to include not only comparative HRQOL evaluations but also utility studies for a more complete picture of the available evidence for therapies in aggressive R/R LBCL.

The scope of this SLR was designed to collect the most relevant evidence for R/R LBCL. The time limitation of 2003 was chosen because the first trial for rituximab, the SOC in newly diagnosed LBCLs, was published in 2002 [3, 63]. As rituximab was not yet established as the SOC for newly diagnosed lymphomas, studies published before 2003 were not likely to include patients with third-line or later lymphoma who were treated with both an anthracycline-containing regimen and a rituximab (or other CD20-targeted agent)-containing regimen.

Challenges encountered during the SLR that limited direct comparison of findings across studies included between-study heterogeneity of populations and methodologies, as well as inconsistent outcome reporting (i.e., outcome definitions, HRQOL measures, follow-up periods, etc.). Despite these limitations, the evidence synthesized in this SLR provides a comprehensive understanding of the HRQOL evidence in R/R LBCL and has identified several sources for utility values in the published literature.

Of note, studies published before and after the 2016 revision of the World Health Organization classification of lymphoid neoplasms may not be directly comparable [64]. Before this revision, LBCLs with *MYC* and *BCL2* and/or *BCL6* rearrangements were considered as "double-/triple-hit lymphomas" and categorized under DLBCL not otherwise specified (NOS) [64, 65]. The 2016 revision reclassified all LBCLs with *MYC* and *BCL2* and/or *BCL6* rearrangements in a single category of "high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements," a distinct entity from DLBCL NOS [64]. Therefore, it is unknown whether studies conducted with patients with DLBCL NOS before this revision included patients with these high-grade B cell lymphomas, which may have impacted the results.

Overall, the evidence synthesized in this SLR provides a comprehensive understanding of the HRQOL evidence in R/R LBCL. A number of cost utility analyses were identified for CAR T cell therapies; novel agents such as polaBR, ofatumumab, and selinexor; and salvage therapies, along with numerous sources for utility values. Consistency in reporting would be beneficial for analyses such as this one, and more HRQOL studies in R/R LBCL are needed to better understand the impact of new therapies on HRQOL.

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Availability of Data and Material Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

Code Availability Not applicable.

Declarations

Conflicts of Interest Fei Fei Liu is an employee of Bristol Myers Squibb and owns stock in the company. Samantha Craigie and Meaghan Bartlett are employees of EVERSANA, which collected consulting fees from Bristol Myers Squibb for their work.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

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